$PM_{2.5}$ and Mortality in Long-term Prospective Cohort Studies: Cause–Effect or Statistical Associations?

John F. Gamble

Exxon Biomedical Sciences, Inc., East Millstone, NJ 08875-2350 USA

Concentrations of ambient $PM_{2.5}$ (particulate matter <2.5 μm in aerodynamic diameter) were associated with increased mortality in two prospective cohort studies. In this paper, I assess whether the weight of the evidence supports a causal association. I assumed the study population in each city to have the same exposure; therefore, these are ecologic studies because exposure is at the group level. Health outcome and confounding data are at the individual level. Ambient PM concentrations are inadequate surrogates for personal exposure because they are at the group level and comprise only a small proportion of personal exposure, they change over time, and they constitute only a small proportion of a life span. The strength of association and exposure–response relationships cannot be determined because the ecologic group-level risks of $PM_{2.5}$ are overestimated 150- to 300-fold based on an analogy with individual-level exposure to inhaled cigarette smoke. Risk estimates may also be high because of confounding from factors such as physical activity and lung function. The evidence is not coherent because the stronger associations are expected to be with morbidity, but instead are with mortality. For example, $PM_{2.5}$ was associated with mortality but not with measurable reductions in lung function. Biological plausibility is lacking because lifetime exposure of rats to combustion products at concentrations two to three orders of magnitude higher than air pollution levels cause lung overloading but no consistent reduction in survival. Criteria for quantitative risk assessment are not met so the data are not useful for setting air quality standards. The weight of evidence suggests there is no substantive basis for concluding that a cause–effect relationship exists between long-term ambient $PM_{2.5}$ and increased mortality. *Key words*: air pollution, causality, confounding, ecological fallacy, ecological studies, epidemiology, particulate matter, prospective cohort, smoking, statistical association. *Environ Health Perspect* 106:535-549 (1998). [Online 5 August 1998]
http://ehpnet1.niehs.nih.gov/docs/1998/106p535-549gamble/abstract.html

In 1997, President Clinton approved an EPA recommendation for a fine particulate matter ($PM_{2.5}$) National Ambient Air Quality Standard (NAAQS) of 15 μg/m^3. Particulate matter less than 2.5 μm in aerodynamic diameter has heretofore been regulated indirectly through regulation of PM_{10}. Fine particulates are generally derived from high temperature processes such as combustion or metallurgical operations emitting vapors, which tend to condense on fine particulate. Tobacco smoke and atmospheric transformation products of SO_2, NO_2, and organics (including biogenic organics) are also mostly in the 0.1–1.0 μm aerodynamic diameter range. The chemical composition tends to be sulfates, acids, metal salts, and carbon. The coarse mode is generally derived from resuspension of soil, industrial dusts, construction, coal and oil combustion, and ocean spray. Composition tends to be flyash (coal and oil), metal oxides, $CaCO_3$, NaCl (sea salt), pollen, mold spores, and plant parts (*1*). The new standard for $PM_{2.5}$ was recommended because of the hypothesis that fine particles "are a better surrogate for those particle components linked to mortality and morbidity effects at levels below the current [PM_{10}] standards" (*2*).

To establish the annual $PM_{2.5}$ NAAQS, the EPA placed great emphasis on two prospective cohort mortality studies: the Six Cities cohort (*3*) and the American Cancer Society (ACS) cohort (*4*). The Six Cities cohort is composed of a random sample of 8,111 white subjects 25–74 years of age at time of enrollment living in six U.S. cities (Steubenville, OH; St. Louis, MO; Portage, WI; Topeka, KS; Waterton, MA; and Kingston/Harriman, TN). Area $PM_{2.5}$ air samples were collected daily from 1979 to 1985, with the mean annual average used as the $PM_{2.5}$ exposure metric. Mortality follow-up was 14–16 years, with a total of 1,430 deaths. The ACS cohort consisted of 295,223 persons recruited by ACS volunteers in the fall of 1982. Vital status follow-up was for 7 years, with a total of 20,765 deaths. Area $PM_{2.5}$ samples in 50 metropolitan areas were collected from 1979 to 1983.

Study results are presented as the risk of mortality (e.g., total, cardiopulmonary) associated with the difference in $PM_{2.5}$ annual concentration between the highest and lowest polluted cities. For example, in the Six Cities study, a 26% increased risk of mortality [relative risk (RR) = 1.26) is associated with an exposure difference of 18.6 μg/m^3 $PM_{2.5}$ (the difference in annual $PM_{2.5}$ between Steubenville, OH and Portage, WI). The results from these two cohorts are summarized in Table 1.

A third cohort study, largely ignored by regulators, consisted of nearly 4,000 nonsmoking Seventh Day Adventists (SDA). In this study, similar in design to the Six Cities and ACS cohort studies, there did not appear to be an association between $PM_{2.5}$ and mortality. Practically no mortality results were reported from this study, but there was extensive reporting on morbidity (*5,6*).

The purpose of this review is to assess whether the weight of the evidence supports a causal association between chronic exposure to fine particulate air pollution ($PM_{2.5}$) and mortality. It is important to understand that the study of air pollution by observational studies is very difficult for a number of reasons, such as the complexity of the air mixture, the highly correlated nature of the pollutants, the relatively low exposure range and weak strength of association in the presence of stronger risk factors, the inability to completely control for confounders, and the lack of individual-level exposure data. These considerations suggest epidemiology may be at its limits (*7*), and it may not be possible to correctly estimate the long-term risk of mortality from PM air pollution from epidemiology studies such as these.

Critique of Studies

The prospective cohort study (as used in the studies reviewed here) is a mixed design incorporating both individual-level data (such as cause of death, age, sex, smoking habits, body mass index, education) and group-level data on ambient air pollution concentrations. Variables that describe

Address correspondence to J.F. Gamble, Exxon Biomedical Sciences, Inc., Mettlers Road, CN 2350, East Millstone, NJ 08875-2350 USA.
Thanks to Mark Nicolich for graphics and discussion of statistics, clarity, and logic, and Vicki Fowler for typing the many drafts.
Received 17 March 1998; accepted 29 April 1998.

PM3001135200

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Table 1. Summary of $PM_{2.5}$ results from the Six Cities (3) and the American Cancer Society (4) cohort studies

Cohort	Deaths (n)	Δ $PM_{2.5}$ (most vs. least polluted city)	Adjusted mortality risk ratios (95% confidence intervals)		
			All causes	Cardiopulmonary	Lung cancer
Six Cities	1,430	18.6 μg/m³	1.26 (1.08–1.47)	1.37 (1.11–1.68)	1.37 (0.81–2.31)
ACS	20,765	24.5 μg/m³	1.17 (1.09–1.26)	1.31 (1.17–1.46)	1.03 (0.80–1.33)

groups of individuals are called ecological, or group-level data. These studies analyze group-level data because there are no individual-level exposure data to any air pollutant for any of the subjects in these studies.

Conceptually, analysis of the data was conducted as if the two studies were experimental studies. In brief, differences in mortality (or survival) between groups (Six Cities, 50 metropolitan areas) were regressed against differences in annual $PM_{2.5}$ while adjusting for differences in risk factors such as age, smoking, body mass index, and education. However, these are observational studies, not experimental studies. Cohort members were not randomly assigned in each city, and it is impossible to achieve between-city similarity in all-important risk factors. There is also not enough information available on each individual to make adequate statistical adjustments for differences in some risk factors. Thus, it may not be possible to reliably estimate the risk associated with between-city differences in $PM_{2.5}$.

These $PM_{2.5}$ cohort studies have generated the hypothesis that long-term exposure to annual $PM_{2.5}$ concentrations at or above about 15 μg/m³ increases total and cardiopulmonary mortality. This hypothesis will be evaluated to determine if it is supported by the evidence, and whether the associations observed are likely to be causal.

This discussion of the scientific evidence will follow a simplified approach that is the logical progression from hypothesis to risk assessment: generate hypothesis → test hypothesis and demonstrate cause–effect → risk assessment.

Testing the hypothesis and establishing causality is a process of developing and assessing the body of data from individual-level epidemiology and experimental studies. Each study must be evaluated regarding its suitability; for example, are individual-level data available for both exposure and response, and is there a lack of significant bias such as from confounding? The suitability of the individual studies will be integrated into the discussion of criteria propounded by Hill (8) for determining whether an association is causal or merely statistical.

The questions of suitability of the individual studies and assessment of a causal versus a statistical association are discussed below.

The section on risk assessment will conclude with a discussion of suggested requirements for epidemiological studies in estimating risk and in developing air quality standards.

Ecologic Study Design

As mentioned above, the prospective cohort study design incorporates individual-level data on cause of death, potential confounders (such as for age, sex, smoking habits, body mass index, education), and group-level (ecological) data on exposure (sulfate and $PM_{7.5}$ in the ACS cohort; total, inhalable and fine PM, sulfates, acidity, SO_2, NO_2, and O_3 in the Six City cohort). The ecological study design is suitable for generating a hypothesis, but is generally not suitable for testing a hypothesis. Weaknesses in the study design and the need for independent confirmation using individual-level data are two reasons that caution in interpretation of ecologic study results is needed.

Weakness of Ecologic Study Design

Ecologic studies are generally considered inferior to individual-level studies because 1) they are subject to biases not present in individual-level studies; 2) the biases in ecologic studies are less well understood; and 3) the effect of biases on risk estimates is unpredictable in ecologic studies.

For example, Brenner et al. (9) showed that while exposure misclassification in individual-level studies often biases the risk estimate toward the null, exposure misclassification in ecological studies may produce extreme overestimates of risk [see also Greenland (10)]. The "ecological fallacy" problem is one of falsely inferring that associations based on group data apply to individuals. That is, there is no way to know if the cohort members who died are also the same individuals who had high exposure to $PM_{2.5}$ relative to those who did not die. The lack of any information on individual-level exposure has led some epidemiologists to conclude that one is "never justified in interpreting the results of ecological analyses in terms of the individuals who give rise to the data" (11).

Temporality. The only causal criterion that must be met is that exposure must precede disease. For chronic disease with long latent periods, exposure must occur years or decades before disease. In these studies it is clear that exposure to ambient $PM_{2.5}$ began at birth, so $PM_{2.5}$ exposure clearly preceded disease. However, the estimates of exposure meet neither of the temporal criteria for latency or precedence. In the Six Cities study, deaths were tabulated for the periods between about 1979 and 1991, and $PM_{2.5}$ data were collected beginning in the late 1970s. For the ACS cohort, vital status was assessed between 1982 and 1989, and fine particulate data were collected from 1979 to 1983. Thus, the exposure in the Six City study was concurrent with the responses. In the ACS cohort, there was inadequate latency because the exposure estimates were collected for no more than 3 years before the response for chronic diseases, which takes decades to develop. In both cases, the temporality criterion was not met.

One could argue that estimated exposure is a surrogate for lifetime exposure and therefore the temporality criterion is met. The following discussion suggests that ambient concentration as used in these studies is not an adequate surrogate for lifetime exposure.

Exposure = Concentration × Time. In both the Six Cities and ACS cohorts, statistically significant associations were reported between mortality (total and cardiopulmonary) and mean ambient $PM_{2.5}$ concentrations and over the concentration range equivalent to the difference between high and low polluted cities. Ideally, one would like to either measure or estimate long-term personal exposure to different air pollutants, i.e., collect individual-level data (12). Measurement of personal exposure as a maximum involves wearing a personal monitor for many years. Estimation of individual-level exposure as a minimum might mean keeping a time–activity diary. What has been used in these studies as a surrogate for exposure is ambient mean concentrations of the geographical areas of the study subjects.

The use of mean ambient air concentration to estimate cumulative long-term exposures in the Six Cities and ACS cohorts is adequate only if several criteria are met.

One criterion is that ambient concentrations should be adequate surrogates for individual exposure. A single monitor for a city population does not provide information on personal exposure. In the sixth year of the Six Cities study, extensive indoor and outdoor monitoring for respirable size particles showed that indoor levels were significantly different from outdoor concentrations, and only a fraction of outdoor respirable PM was penetrating indoors. The differences were such that people "living in

PM3001135201

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Table 2. Demonstration of ecologic fallacy in comparisons of individual-level and group-level mortality risk estimates

Results	Exposure (μg/m³)	Total mortality RR	Total mortality Risk/ 20 μg/m³	Total mortality Toxicity of $PM_{2.5}$ vs. tobacco smoke[a]	Cardiopulmonary mortality RR	Cardiopulmonary mortality Risk/ 20 μg/m³	Cardiopulmonary mortality Toxicity of $PM_{2.5}$ vs. tobacco smoke[a]
Group level(ecological):							
ambient $PM_{2.5}$							
Six Cities	18.6	1.26	1.28	299	1.37	1.40	339
ACS	24.5	1.17	1.14	147	1.31	1.25	225
Individual-level (cohort):							
25 pack-year smoker (average tar)							
Six Cities	16,700	2.00	1.0008[b]	–	2.30	1.001[b]	–
ACS	16,700	2.07	1.0009[b]	–	2.28	1.003[b]	–

Abbreviations: RR, relative risk; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; ACS, American Cancer Society. See Appendix A for further calculations.

[a]Toxicity of $PM_{2.5}$ versus tobacco smoke: divide estimate of group-level (GL) $PM_{2.5}$ risk per 1 μg/m³ (= group-level coefficient) or β_{GL} by estimate of individual-level (IL) tobacco smoke risk per 1 μg/m³ tar for (β_{IL}), or β_{GL}/β_{IL}. For example, using total mortality in the Six Cities study: β_{GL} = ln RR 1.26/18.6 μg/m³ = group-level β coefficient for $PM_{2.5}$ and total mortality in the Six Cities study; β_{IL} = ln RR 2.00/16,700 μg/m³ = individual-level β coefficient for cigarette smoke; β_{GL}/β_{IL} = 299.

[b]If $PM_{2.5}$ were as toxic as tobacco smoke, what would RR be? To estimate β coefficient for tobacco smoke (β_{IL}), multiply by $PM_{2.5}$ exposure difference between high and low polluted cities, and calculate RR. For example $e^{(\beta_{IL} \times 18.6\ \mu g/m^3)} = 1.0008$ for total mortality in the Six Cities study.

a 'clean' city, as defined by ambient levels, may be exposed to levels comparable or higher than those of people living in a 'polluted' area due to indoor air pollution levels. In this way subjects [in the Six Cities cohort] may be misclassified as to exposure," and bias the results because it is not known whether those who died were also exposed to higher levels of $PM_{2.5}$ (*13*).

In one of the Six Cities (Kingston/Harriman), personal exposures were higher, had a greater variance than outdoor concentrations, and were uncorrelated with outdoor concentrations (*14*).

Data from other cities also show that outdoor concentrations are poor surrogates for personal exposure. Ozkaynak et al. (*15*) concluded that outdoor sources in Riverside, California, could only explain about 16% of the variance in personal exposure; thus, it "does not seem possible to use outdoor measurements alone to reliably predict personal exposure to PM_{10}." Mage and Buckley (*16*), in a review of the relationship between personal PM and ambient PM, concluded that variations in ambient PM "may have small influence" on individual personal exposure. Further, this lack of correlation has "significant implications" for "an ecological relation... in a community [time–series] or between communities [prospective]" (*16*). Brown et al. (*17*) reported undetectable to weak or marginal associations between personal exposure and outdoor concentrations of PM_{10} and $PM_{2.5}$ in four U.S. cities, and study subjects in two of the cities (Nashville and Boston) had moderate to severe chronic obstructive pulmonary disease. These authors concluded that the inability to reliably predict personal exposures based on outdoor concentrations is inconsistent with a causal association.

Ambient PM as surrogate for total PM exposure (EPA argument). Average ambient $PM_{2.5}$ concentration was used as one of the indices of "exposure to combustion source ambient particulate air pollution" (*4*). The EPA (*18*) suggested that ambient PM is an appropriate surrogate, that it adequately characterizes personal exposure to ambient PM, that there is a clear "relationship between health outcomes and ambient PM concentrations," and, therefore, it is "reasonable to presume that reduction in ambient PM will help to protect the public from adverse health effects associated with personal exposure to ambient PM."

The EPA (*18*) argued that nonambient PM exposures vary independently of ambient PM. Ambient PM is "expected to be a major portion of the ambient PM measured in a person's residential area" and is expected to be a major portion of personal exposure. Thus, nonambient PM "would probably not be a confounder in epidemiology studies" but could be an independent risk factor (*18*). Because ambient PM is not correlated with nonambient PM, "epidemiological studies relating health outcomes to ambient PM would not provide any information about the health effects that may be caused by [nonambient] PM" (*18*). The only salient factors then, are that "there is a relationship between health outcomes and ambient PM," and there is a relationship between "ambient PM... and personal or population exposure to ambient PM" (*18*).

There are two crucial assumptions in this argument: one is that ambient PM must constitute a major proportion of total PM exposure, and the second is that there is a constant proportionality between ambient and personal exposure to PM. While these assumptions may be met for nonsmokers living in residences without major indoor PM sources, they are not met for a large proportion of the rest of the population, in particular, the populations studied in the ACS and Six Cities cohorts.

Table 3. Statistics from stepwise regressions identifying significant independent variables in predicting the dependent variable personal exposure

Level	R^2	Independent variables
1	<1%	Ambient PM
2	16%	Ambient PM + cigarette smoke
3	17%	Level 2 + time at home, time at work, time traveling, time in public, other time
4	51%	Level 3 + indoor PM

Data from Spengler et al. (*14*).

The basis for these conclusions can be derived from the argument developed by the EPA (*19*) and outlined below [comments in brackets have been added by the author]:

1. Personal exposure to total PM is a critical parameter when analyzing individual health outcomes. [To use group-level exposure data in place of individual-level data can produce biased results characteristic of the ecologic fallacy. Also, see Table 2.]
2. Ambient PM is a surrogate for personal total PM exposure and therefore is a secondary surrogate for PM dose.
3. Ambient PM is a suitable surrogate to personal exposure "if ambient concentration was also linearly related to the personal exposure." However, treating ambient PM as a "surrogate for total exposure to PM from all sources... would be wrong. [The EPA also argues that ambient PM and nonambient PM vary independently, in which case the relationship cannot be linear. Thus, the concepts of independence and linearity of ambient and nonambient PM are incompatible.]
4. Personal exposure to PM of ambient origin is a poor surrogate for total personal PM exposure (ambient PM + indoor PM) "for those people whose personal exposures are dominated by indoor (residential and occupational) sources such as environmental tobacco smoke (ETS)."

PM3001135202

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

ETS adds on the order of 25–45 μg/m^3 to 24-hr average personal exposures and residential environments where smoking takes place.

Spengler et al. (*14*) compared personal exposure measurements to simultaneously collected home and outdoor concentrations of respirable particulates in Kingston, one of the towns included in the Six Cities study. Step-wise regression models were evaluated to identify significant predictors of personal exposure. The square of the multiple correlation coefficient (R^2) was used to evaluate predictive power. R^2 values can range from 0% to 100%, and the larger the R^2, the greater the predictive value. For example, in the Level 1 model (see Table 3), ambient PM alone explained <1% of the variance in personal exposure, so this model had "no predictive power." Three additional predictive models (Levels 2 through 4) were analyzed. By adding more independent variables, the R^2 values increased.

Indoor PM alone explained 47% of the variance of personal exposure overall. The predictive power of the fourth-level model varied with different subgroups in the population (i.e., 20% for employed subjects from nonsmoking households to 84% for nonemployed subjects from nonsmoking households). Spengler et al. (*14*) concluded that "misclassification and misassociation of exposures...are likely to result...[when] relying upon ambient community-based particle measurements."

Smokers are usually excluded in these assessments, and personal monitors do not measure directly inhaled mainstream tobacco smoke. Thus, nonsmokers comprise essentially the only group for which correlations of ambient/personal exposure have been assessed (*19*). For many nonsmokers, ambient PM comprises only a small proportion of personal PM exposure, thus the first critical assumption is not met.

5. For a smoker, ambient PM concentration is an even poorer surrogate for personal exposure because the several milligram amounts of directly inhaled cigarette smoke by an average smoker "can be two to three orders of magnitude greater" than the microgram amounts of ETS that the personal monitor captures (*19*). The personal exposure of "dusty-trade workers can also be several orders of magnitude greater than their exposure to indoor particles of ambient origin" (*19*). The "inhalation of mainstream tobacco smoke will be a major additive exposure to PM for the smokers, which dwarfs the nonsmokers" personal exposure monitor PM exposure (*19*). A major proportion of the U.S. population (e.g., smokers) has a total exposure to PM that is at least "one order of magnitude greater" than that of the nonsmokers (*19*). [Thus, ambient PM comprises a negligible fraction of total personal exposure to PM and is not linear when nonsmokers, exposed nonsmokers, and smokers are considered.]
6. If the variance of personal PM exposures, which is uncorrelated to ambient PM (e.g., from indoor sources, traffic, occupational, ETS) among nonsmokers, is very large, the percentage of the variance of personal PM that can be explained by the variance in ambient PM will be very small (*19*). [This is the case in most of the studies cited by the EPA (*19*) in their Table 7-26. When personal exposure to mainstream tobacco PM is taken into account, ambient PM explains even less. Inhalation of mainstream tobacco smoke outweighs the sum of all other indoor and outdoor PM exposures and "may have an important implication for interpretation of epidemiology studies that relate ambient PM...to mortality or morbidity" (*19*)]. Ambient PM is a surrogate for personal exposure to ambient PM, but because ambient PM comprises a variable, and often quite small, proportion of total personal exposure to PM, it "would be wrong" to treat ambient PM as a surrogate for total personal exposure to PM (*19*). [To consider ambient PM without considering personal exposure to PM is also wrong.]

In sum, total personal exposures to $PM_{2.5}$ are critical in assessing the association of PM exposure and mortality and morbidity. If ambient $PM_{2.5}$ is a surrogate for total personal exposure [as argued by the EPA (*19*)], then ambient $PM_{2.5}$ should be linearly related to personal exposure and not be "dwarfed" by nonambient sources of $PM_{2.5}$. Because neither of these assumptions is satisfied for a "large proportion of the population," ambient PM is not an adequate surrogate exposure variable.

Lifetime estimates of exposure. Another criterion necessary for valid use of ambient concentrations as long-term estimates of cumulative exposure is that ambient concentrations must have remained relatively constant for several decades. Outdoor concentrations in the Six Cities and ACS cohorts are available for only a few years. During the lifetime of cohort members, ambient concentrations were changing and were probably higher in the past than recently. For example, in the ACS cohort, the 1979–1983 ambient concentrations were considered representative of long-term cumulative exposure, but they are unlikely to be representative of dirtier cities for even the previous decade, when there was extensive cleanup. The total suspended particulate (TSP) was reduced by a factor of two in New York City, for example (*19*). Darlington et al. (*20*) reported that there were significant reductions in PM_{10} from 1988 through 1995. Nationwide, the weighted annual average was reduced about 24% (34 μg/m^3 to 26 μg/m^3). In nonattainment areas, the 7-year reduction was about 25%, compared to about 20% in attainment areas. The average reduction in the anthropogenic portion of PM_{10} (primarily $PM_{2.5}$) is between 27% and 33%. The effect of an underestimate of exposure concentration is to spuriously inflate the risk estimate.

Geographic mobility. A third criterion is that account should be taken of both long-term and short-term geographic mobility. Long-term mobility refers to moves of residence or workplace to different cities. Short-term mobility refers to working at a location different from one's residence for each working day, and not working on weekends (*12*). Geographic mobility has been addressed in the SDA cohort by interpolating monthly monitor data to the zip codes of the home and work locations (*5,6*).

A related criterion is that exposure estimates should include a significant portion of each individual's life span. This is not the case because of the limited time period when $PM_{2.5}$ was sampled. The ambient $PM_{2.5}$ concentrations were only measured for 6–9 years in the Six Cities study and 4 years in the ACS study. For a person 74 years old at entry into the Six Cities cohort who died the first year of follow-up, ambient $PM_{2.5}$ concentrations would be for 2 years (1977–1979) or 2.5% of lifetime, and part of the association would be for exposures occurring after death. For a person 25 years old at entry who died at the end of follow-up (age = 40 years), ambient $PM_{2.5}$ concentrations would be available for 10 years (25% of lifetime). In the ACS cohort, the cumulative exposure is only available for the years 1979–1983 and follow-up is for September 1982–December 1989. The minimum and maximum fraction of lifetime for which ambient concentrations are available are less than 1.4% (for a 74-year-old at entry who died in 1982) and 11% (for a 30-year-old at entry who died in 1989 at end of follow-up).

Finally, account should be taken of differing individual lifestyles, such as time spent outdoors. This problem has been addressed in the SDA cohort by adjusting ambient mean concentrations to reflect time spent indoors and in transit according to indoor penetration factors (*12*).

PM3001135203

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Summary. In summary, the Six Cities and ACS prospective cohort studies are unable to evaluate the effects of long-term exposure on mortality because 1) ambient concentrations were not measured long enough before death to meet the temporality criterion for causality; 2) ambient PM is only a small proportion of total PM exposure for the majority of the population and will therefore be overwhelmed by effects of total PM exposure; 3) ambient PM concentrations have declined for the last several decades; 4) lifetime residences are not known; and 5) there are no available estimates of long-term cumulative exposure as ambient concentrations are available for only a fraction of a lifetime (range of <2%–25%).

The group-level estimates of $PM_{2.5}$ exposure compared to lifetime cumulative exposure to tobacco smoke in the Six Cities and ACS cohorts show a marked difference in both the adequacy of the exposure estimates and in the estimated toxicity of $PM_{2.5}$. The (concentration × time) exposure metric for tobacco smoke is in pack-years. In both the Six Cities and ACS cohorts, the risk ratios (RR) for smokers were estimated for a 25 pack-year smoker. These data will be used to test the $PM_{2.5}$ hypothesis by comparing estimated risk of ambient $PM_{2.5}$ air pollution with that of tobacco smoke.

Lack of Consistency and Demonstration of Ecologic Fallacy

To verify findings based on the ecologic study design, individual-level exposure data in studies relatively free of bias are needed (*9,11,21,22*). Such a comparison of individual-level study results was implied in Hill's (*8*) consistency criterion for causality and demonstrated in the consistent associations from over 30 individual-level cohort and case–control studies of mortality and smoking in the 1964 Surgeon General's report on smoking (*23*). Individual-level studies relatively free of bias will be the standard used to evaluate the validity of the $PM_{2.5}$ group-level risk estimates. Such a reference standard should meet several requirements:

- Individual-level data should be available for both exposure and mortality. It is helpful that both are available for smokers in the Six Cities and ACS cohorts.
- A causal association should be well established.
- Fine particulate matter from combustion is a relevant type of PM, as it is considered among the most toxic components of $PM_{2.5}$ air pollution.

Tobacco Analogy

Studies of mortality and tobacco smoking meet the above requirements and provide an appropriate standard for confirmation or invalidation of the group-level $PM_{2.5}$ risk estimates.

Individual-level estimates of risk. Individual-level risk estimates of the association between mortality (both total and cardiopulmonary) and cigarette smoke are available from both the Six Cities and ACS cohorts.

Individual-level exposure to fine PM from smoking a cigarette can be estimated based on the following reasoning.

In 1957 the average tar content was 35 mg/cigarette (*24*). Tar content is defined by the Federal Trade Commission (FTC) as the total particulate in mainstream smoke minus water and nicotine and is determined by smoking cigarettes under standard conditions in a smoking machine. The typical smoker in 1980 smoked 32 cigarettes/day and inhaled 448 mg tar/day (14 mg/cigarette × 32 cigarettes/day) (*25*). At 18 m^3 air breathed per day, the equivalent average ambient $PM_{2.5}$ concentration was 24,900 $\mu g/m^3$. [A time-weighted average 24-hr mean concentration is also an average long-term exposure of a smoker compared to nonsmoker and is analogous to the difference in annual ambient $PM_{2.5}$ concentrations between the most polluted city versus the least polluted city.] In 1986, about 47% of smokers bought high-tar cigarettes (≥15 mg) and <3% bought very low-tar cigarettes (<3 mg).

Analysis of tar content is usually based on results from machine smokers, which may underestimate tar content. For example, the FTC method smokes at one puff/minute, while the average smoker inhales about two puffs/minute (*26*).

The range of tar in cigarettes is quite wide, from a low of about 0.5 mg to above 35 mg. For comparison of group and individual-level risks, smoker exposures to cigarettes containing 0.5 mg and 15 mg were selected for illustrative purposes to provide a range of estimates of exposure. The low-tar cigarette provides the most conservative estimate because it is smoked by only a small proportion of smokers and has been marketed for a relatively short time. At the approximate midpoint of the Six Cities study update, the average tar content might have been about 15 mg/cigarette or higher. Using a 15-mg tar cigarette as an average for illustrative purposes underestimates average exposure and is also a conservative approach to illustrating the differences between group-level and individual-level estimates of risk. In the examples in this report, 20 cigarettes/day will be used because RRs in the Six Cities cohort were for a smoker with 25 years of smoking 20 cigarettes/day (and 25 pack-years in the ACS cohort) compared to a nonsmoker. [Smokers who switch to lower (or higher) tar cigarettes tend to take in somewhat less (or more) PM, but less (or more) than expected because of compensation (*27*).]

Tobacco smoke contains fine combustion particulate. Ambient $PM_{2.5}$ is considered a combustion source particulate air pollutant, and combustion source particulates are considered important contributors to early mortality (*4*).

Cigarette smoke PM is also a combustion product and is a fine particulate of respirable size, much of it of submicron size. Particle sizes reported in the literature range from 0.25 to 0.7 μm by mass median aerodynamic diameter and from 0.15 to 0.35 μm by count. Virtually 100% of smoke particles are in the respirable range (*28*).

Mortality is well characterized. The risk of mortality from tobacco smoke is well characterized in dozens of individual-level studies as summarized in the Surgeon General's reports on smoking (*23,26*), and the causal association between smoking and a number of diseases is generally accepted.

Demonstration of Ecologic Fallacy

Because a "gold-standard" (individual-level epidemiology studies of smokers) is available, we can now address the question: Are group-level risk estimates of $PM_{2.5}$ toxicity from the Six Cities and ACS cohorts comparable to individual-level risk estimates of $PM_{2.5}$ from cigarette smoke for total and cardiopulmonary deaths?

The relative risks of total mortality for 25 pack-year smokers and an annual estimated exposure of approximately 16,700 $\mu g/m^3$ is 2.00 and 2.07 in the Six Cities and ACS studies, respectively. For cardiopulmonary mortality the RR are 2.30 and 2.28, respectively. These risks are based on individual-level exposure data and should be considered the reference value. Group-level estimates of risk for total mortality in the Six Cities and ACS cohorts are 1.26 and 1.17, respectively, for an estimated $PM_{2.5}$ exposure of about 20 $\mu g/m^3$. For cardiopulmonary mortality the group-level RR are 1.37 and 1.31, respectively.

Group-level estimates of risk suggest that $PM_{2.5}$ is about 150–>300 times more toxic than individual-level estimates of tobacco smoke toxicity. If $PM_{2.5}$ were as toxic as tobacco smoke, the effect of a 20 $\mu g/m^3$ difference in $PM_{2.5}$ exposure would be too small to measure (Table 2; see also Appendix 1 for further discussion of these calculations).

The individual-level risks of exposure to various pack-years of smoke (current smoker, former, ever smoker) were also tabulated in

PM3001135204

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

the Six Cities and ACS cohort studies and are compared to estimated group-level risks of ambient $PM_{2.5}$ (Fig. 1 and 2). The overestimates of group-level risks are clearly seen, especially in the ACS study where never smokers have a slightly higher risk than ever smokers although ever smokers have an added burden of nearly 20,000 μg/m³ tobacco smoke exposure (Fig. 2).

These data suggest that the true risk of mortality from $PM_{2.5}$ air pollution is unknown and probably unmeasurable. The estimated group-level risks of 1.17–1.40 are small but are not negligible, as expected if $PM_{2.5}$ were as toxic as mainstream tobacco smoke. Nevertheless, they are implausibly large compared to the smoking risk estimate of 2.0–2.3, considering that smokers are exposed to a presumably more toxic particulate at concentrations over three orders of magnitude higher.

The group-level $PM_{2.5}$ risk estimates from the Six Cities and ACS cohorts are so much larger than the reference values that the hypothesis is not confirmed, the test for consistency is not met, and the $PM_{2.5}$ risk estimates from group-level data are invalidated. If $PM_{2.5}$ were as toxic as tobacco smoke, the differences in exposure between cities would be too small to measure effects on mortality. $PM_{2.5}$ could be more toxic than tobacco smoke, but there is no evidence for this and it seems unlikely.

Interrelationships of Strength of Association, Exposure–Response, and Confounding

The presence of a strong association and a biological gradient (exposure–response; E-R) are supportive of a causal association. A weak association is one in which the ratio of the frequency of mortality between high and low exposed groups is small in magnitude. A risk ratio of about 1.50 (i.e., 50% increase) is a weak association (*29*). In the Six Cities and ACS cohorts, differences between cities of 20 μg/m³ were associated with 28% and 14% increases in total mortality, respectively. This 20-μg/m³ difference in concentration between high and low polluted cities is about 0.1% of $PM_{2.5}$ exposure experienced by an average smoker. Although the group-level estimates suggest that $PM_{2.5}$ may be several orders of magnitude more toxic than tobacco smoke, the exposure range is still too narrow to reliably measure an effect, even at a high level of toxicity.

For an association to be reliable, it must also be relatively free of confounding. If confounding is present, particularly when the association is weak, then the true E-R association may be indeterminable. The weaker an association, the more likely it is that bias, confounding, or inappropriate analysis may explain the association, and the greater the need for a thorough understanding of the underlying biological mechanisms (*30*).

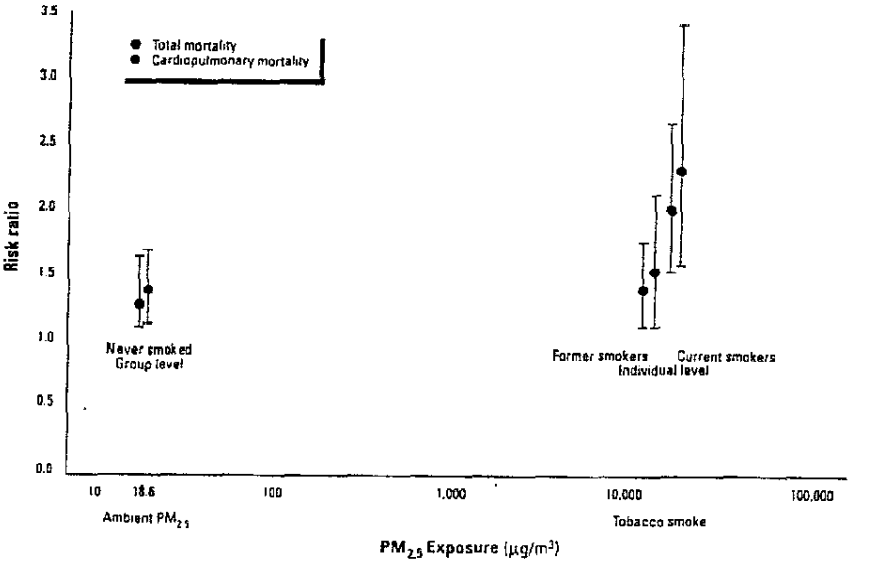

Figure 1. Six Cities study: total and cardiopulmonary mortality rate ratios (individual-level versus group-level estimates). Tobacco smoke $PM_{2.5}$ is from 15 mg tar/cigarette with 20 pack-years for former smokers and 25 pack-years for current smokers. Error bars indicate 95% confidence intervals.

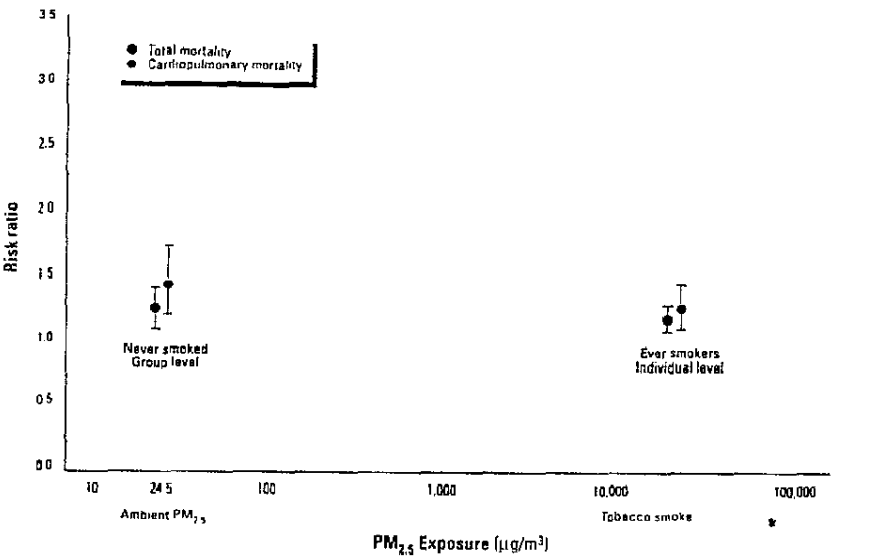

Figure 2. ACS cohort: total and cardiopulmonary mortality rate ratios (individual-level versus group-level estimates). Tobacco smoke $PM_{2.5}$ is from 15 mg tar/cigarette with 29.8 pack-years for ever smokers. Error bars indicate 95% confidence intervals.

Confounding

Confounding in these studies can occur because of initial differences in major risk factors between the cohorts in each city. In the cohort study the mortality in different study populations is compared and the differences correlated with average PM of each study population. Major risk factors associated with increased mortality should be similar among all study subjects and, if not, they should be adjusted for in the analysis. The analyses are similar to an experimental study in which all exposure groups (or cohorts in each city) are considered identical except for exposure to particulate matter.

Thus, confounders in the cohort study are often different than in the time–series studies where the changing mortality is correlated with changes in PM in a constant study population. Important potential confounders

PM3001135205

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

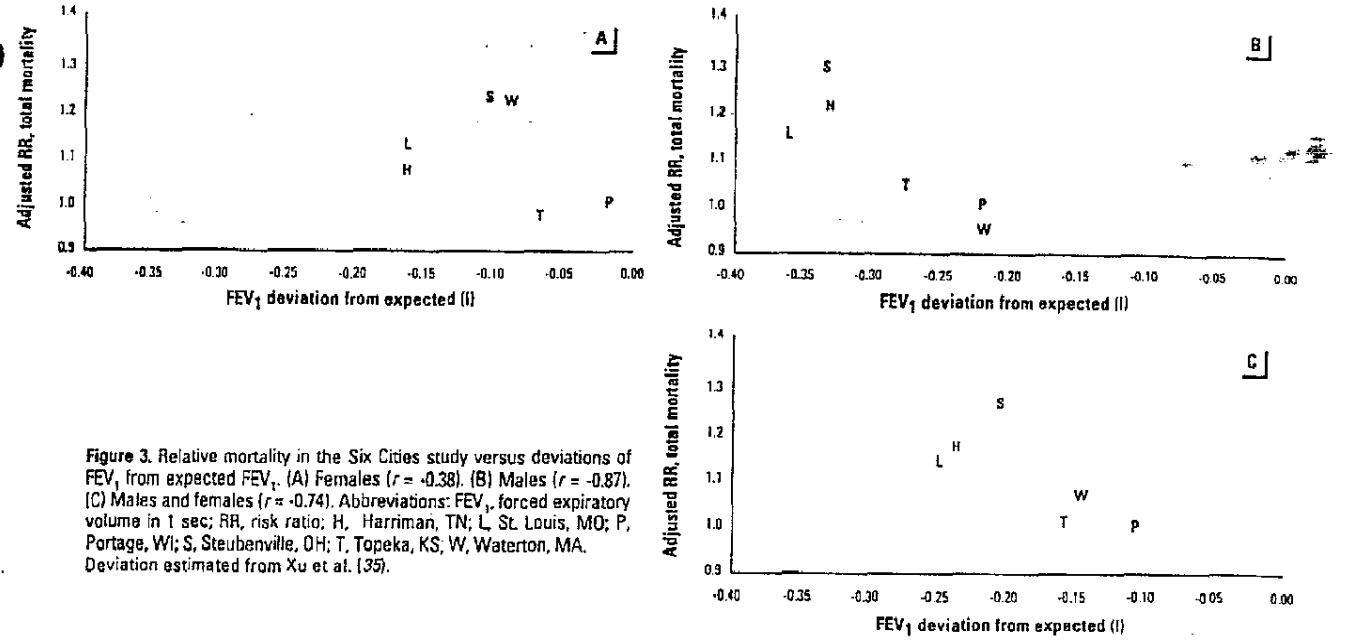

Figure 3. Relative mortality in the Six Cities study versus deviations of FEV_1 from expected FEV_1. (A) Females (r = -0.38). (B) Males (r = -0.87). (C) Males and females (r = -0.74). Abbreviations: FEV_1, forced expiratory volume in 1 sec; RR, risk ratio; H, Harriman, TN; L, St. Louis, MO; P, Portage, WI; S, Steubenville, OH; T, Topeka, KS; W, Waterton, MA. Deviation estimated from Xu et al. (*35*).

in the time–series studies include weather (and factors that vary with PM). Important potential confounders in the cohort studies are differences in the distribution of risk factors among the cohorts in each city, such as diet, socioeconomic status (SES), lung function, physical activity, blood pressure, etc.

The objective that cohort members from each city be essentially the same for all important risk factors except for ambient $PM_{2.5}$ is not achieved, so there is confounding. Two examples are discussed below.

Lung function. One example of confounding is lung function, specifically forced expiratory volume in 1 sec (FEV_1). Reduced FEV_1 is a risk factor for total, respiratory, and cardiovascular mortality, even among nonsmokers. In an 18-year prospective study of nonsmokers, the RRs associated with a 1-liter decrease in FEV_1 were 1.52, 4.16, and 1.49, respectively, and FEV_1 was a stronger predictor of mortality than body mass index or plasma cholesterol (*31*). In a 30-year follow-up of men in Boston, Massachusetts, a reduction of 1 liter in FEV_1 was associated with a 70% increase in total mortality and was a more significant risk factor than current smoking, total cholesterol, blood pressure, or body mass index (*32*).

FEV_1 varies by smoking category and by sex between cities in the Six Cities study. Nevertheless, the between-city differences in FEV_1 are not due to differences in $PM_{2.5}$ pollution. For example, the adjusted differences between nonsmokers in Steubenville and Portage is 0.18 liters (*33*). For ex-smokers, the differences in FEV_1 for males and females are 0.115 and 0.160, respectively, and for a smoker of a pack per day or more are 0.112 and 0.145 liter, respectively [estimated from data of Ferris et al. (*34*)]. Figure 3 graphically displays the potential effect of differences in FEV_1 between cohort members in the Six Cities study. These are not precise estimates because the distribution of smokers in each city was not available, so it was necessary to assume the same distribution of smokers in each city (*35*). These results indicate that lung function is a probable confounder.

Sedentary living. Another example of unadjusted confounding is sedentary living. Lack of exercise is an independent risk factor for mortality. The population attributable risk (PAR) is 13% for sedentary living (*36*).

Lipfert (*37*) evaluated mortality risk as a function of sedentary lifestyle in five of the six cities and showed that it alone appeared to be as good a predictor of mortality as $PM_{2.5}$. In a similar analysis, Lipfert (*37*) plotted age and race-adjusted mortality versus $PM_{2.5}$ for areas that roughly corresponded to the 50 locations in the ACS study. By adding additional nonpollutant confounding variables (smoking, education, overweight, ethnicity, water hardness, sedentary lifestyle, poverty, migration) the E-R slope was reduced considerably. Because sedentary lifestyle was not adjusted for in either study, it could possibly be the cause of the apparent E-R trends for $PM_{2.5}$.

Other considerations. It is important to note that information on potential confounding variables in the Six Cities and ACS cohorts included only age, sex, race, smoking, education, overweight, exposure to passive smoke, and alcohol; in the ACS study, occupational exposure was also included. Adjustment may be inadequate for some of these. For example, nonlinear instead of linear relationships may be more appropriate for weight and alcohol; education is not a good surrogate for SES of women, etc. The EPA (*19*) also indicated that spatial confounding from unadjusted confounders, as well as linear modeling for nonlinear effects, has resulted in overestimates of risk.

Lipfert (*37*) concluded that the differences in mortality between cities are, in part, dependent on the number of possible confounders in the model. Thus, the associations in the six cities and ACS cohort studies may be due to the lack of adjustment for important confounding variables and not due to $PM_{2.5}$. The adjustments by Lipfert (*37*) are based on group-level data; however, the lung function data from the Six Cities cohort are individual-level data.

There may be other more appropriate ways to assess strength of association and causality. A single outcome, such as mortality, has multiple causes that relate to an individual's total life history. Multiple causes range from genotype and developmental history to such risk factors as smoking, diet, physical activity, and work and living environment. The important question is: What

PM3001135206

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

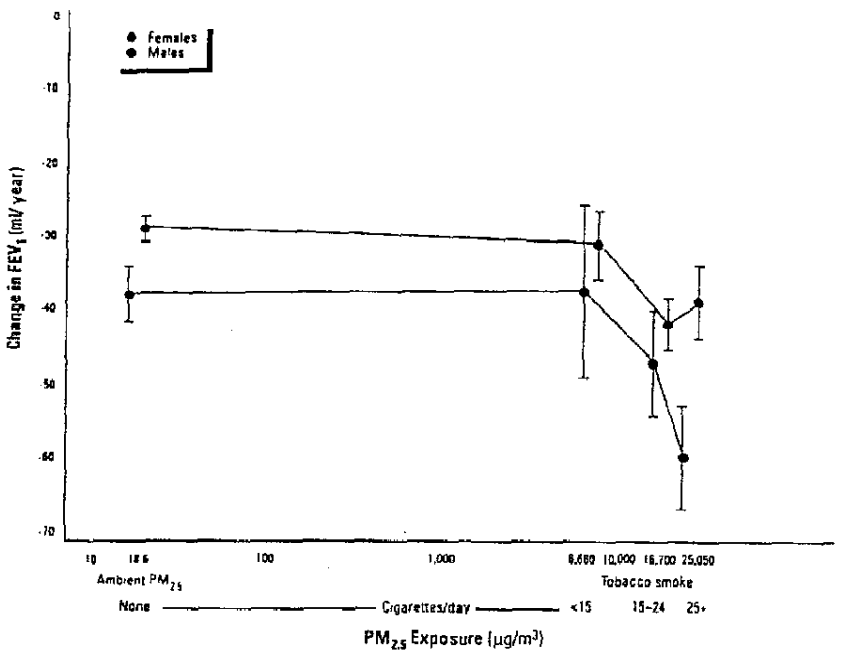

Figure 4. Six Cities study: differences in FEV_1 between cities are not due to differences in $PM_{2.5}$. FEV_1, forced expiratory volume in 1 sec. The change in FEV_1 was estimated from Xu et al. (*35*).

major factors affect mortality, and what is their relative importance?

For example, Spengler et al. (*14*) used stepwise regression models and R^2 to assess the relative importance of ambient PM, indoor PM, and time–activity patterns in predicting personal exposure. Dockery et al. (*3*) separated the data according to smoking status, sex, and occupational exposure and then evaluated the effect of these covariates on the adjusted risk ratio for $PM_{2.5}$. However, risk ratios were used instead of the more informative R^2 values. These efforts are a step in the direction of a more global assessment of important determinants of mortality.

It is not clear whether all possible combinations were evaluated, and in the Six Cities study not all risk factors (such as FEV_1) were included in the analyses. It is also not clear why ambient PM is noninformative regarding personal exposure, but is a significant variable associated with mortality in the Six Cities study. A more appropriate and informative approach is needed to achieve greater understanding of the importance of these risk factors. Use of an approach such as regression trees would be an improvement because it allows possible combinations to be identified in a model-free, tiered approach so the predictive power of all variables can be evaluated.

Given the very weak association with $PM_{2.5}$ and lack of adjustment for important confounders, the true E-R relationship between $PM_{2.5}$ and mortality cannot be determined in the Six Cities and ACS cohort studies.

Coherence

Do the data conflict with generally known facts of the disease? Are other health effects observed? Are the ecologic risk estimates coherent and consistent with individual-level risk estimates?

Two approaches are taken in addressing coherence. The first and most important is to assess coherence of individual-level lung function data, comparing the known effects of tobacco smoke exposure to the predicted effects of $PM_{2.5}$. The second approach is two sided. On the one hand, I argue that coherence cannot be assessed using other ecological study designs, either time–series or cohort. But, if one thinks ecologic study results can be used to support other ecological study results, then the SDA cohort is the appropriate study because both mortality and morbidity data are available.

Arguing Coherence Using Individual-level Studies: Tobacco Analogy

Several examples follow of how the Six Cities study conclusions on mortality are not coherent with other knowledge, even with individual-level morbidity data on lung function from the Six Cities study population.

An appropriate place to evaluate coherence is to evaluate changes in morbidity within the cohorts. Again the tobacco analogy is useful, this time for assessing the effects of tobacco smoke on changes in lung function. Xu et al. (*35*) examined the lung function of Six Cities cohort members on three occasions over a 6-year follow-up period. Loss of pulmonary function [FEV_1 and forced vital capacity (FVC)] depended "linearly on the number of cigarettes smoked each day." Adjusted reduction in FEV_1 and FVC in men and women smoking 30 cigarettes/day ranged from 4.1 ml/year to 12.6 ml/year. For 5 cigarettes/day (or about 4,000 μg/m³/day exposure), the estimated yearly change would be negligible (<1 ml). The possible lack of a smoking effect among lighter smokers is also supported by the similarity in age-adjusted average rate of change in FEV_1 between nonsmokers and less than 15 cigarettes/day smokers (see Fig. 4).

While these results may not be conclusive for lifetime exposures because of short follow-up, relatively high dropout rate, small numbers, and variability in the data, the results suggest that $PM_{2.5}$ in ambient air is unlikely to produce larger reductions in FEV_1 than those experienced by a light smoker exposed to about 6,000 μg/m³ tobacco smoke during the period of this study. These data also suggest that the differences in FEV_1 between cities are not due to the small differences in ambient $PM_{2.5}$. The lack of an apparent effect on FEV_1 for light smokers is not coherent with an increase in mortality associated with much smaller exposures to $PM_{2.5}$ air pollution.

Lifetime smoking data indicate a linear relationship between cumulative cigarette smoking measured as pack-years and irreversible loss of FEV_1 and FVC in the Six Cities study (*38*). The irreversible effect of cumulative pack-years on height-adjusted FEV_1 is 7.4 ml/pack-year (~0.0004 ml/μg/m³ cigarette smoke), plus an additional reversible deficit of 123 ml for a total of 308 ml over 25 years for a pack/day smoker. For a 25 pack-year woman smoker, the estimated effect of cumulative smoking is 110 ml plus a reversible deficit of 107 ml, for a total of 217 ml. This is about 9% of mean height-adjusted FEV_1 at 50 years of age. If ambient $PM_{2.5}$ air pollution is as toxic as cigarette smoke (and nonsmokers have a similar response as smokers), an 18.6 μg/m³ exposure for 25 years would result in irreversible loss of about 0.208 ml and a reversible deficit of about 0.139 ml, or a total of 0.347 ml. The equivalent losses for women are 0.124 ml, 0.121 ml reversible, or 0.245 ml total.

These estimated losses in FEV_1 from 25 years exposure to an annual average of 18.6 μg/m³ are much less than 1% of height-adjusted FEV_1 and are too small to measure with reliability. These results are not coherent

PM3001135207

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

with the group-level estimates of mortality, as one would expect a larger effect on morbidity than mortality.

Gori and Mantel (*39*) suggested the threshold at which significantly increased risks of lung cancer, coronary heart disease, and respiratory disease mortality can be detected are about four to five cigarettes per day. This is an average exposure of about 3,300–4,200 $\mu g/m^3$ for a 15-mg tar cigarette, or 150–210 times greater than the difference between high and low polluted cities. These individual-level estimates of risk from cigarette smoke are also not coherent with the group-level estimates of risk from $PM_{2.5}$.

Arguing Coherence Using Time–Series Studies

Pope et al. (*4*) state that time–series studies show that particulate air pollution is associated with declines in lung function, increased respiratory symptoms, respiratory hospitalizations, restricted activity due to respiratory illness, and increased mortality, especially respiratory and cardiovascular mortality. They suggest this "coherent cascade of cardiopulmonary health effects" enhances biological plausibility of the cohort mortality studies.

Use of time–series studies to support the coherence criterion is not appropriate. The questions addressed by time–series and prospective studies are different. Time–series studies attempt to answer whether individuals already sick with preexisting cardiorespiratory illness die because of episodes of short-term elevations in air pollution. Prospective cohort studies address the question of whether long-term exposure of primarily healthy individuals increases the risk of total and cardiopulmonary mortality. Dockery et al. (*3*) concluded that "because the daily time–series studies evaluated only the effect of short-term changes in pollution levels, whereas our study [Six Cities] evaluated associations with long-term exposure..., quantitative comparisons with these investigations are difficult to make."

Arguing Coherence Using Other Group-level Studies

It is a circular argument to use other ecological studies to test or validate either the consistency or coherence criteria. Ecologic studies are subject to similar biases and, in general, lack the rigor to test the hypothesis. If one does not accept this reasoning and uses ecological studies to assess the coherence criterion, the SDA cohort study and lung function data on children in the Six Cities study are the logical places to address the question of whether both mortality and morbidity are associated with PM in the same cohort.

Table 4. Symptom changes in the Seventh Day Adventist study, 1977–1987

	RR	New cases (*n*)	Persistent (*n*)	Reversal (*n*)	Percent reversal
AOD	$p<0.05$	330	317	163	34%
Asthma	$p>0.05$	87	126	130	51%
Chronic bronchitis					
Cough type	$p<0.05$	180	125	107	46%
Sputum type	$p<0.05$	281	157	139	47%

Abbreviations: RR, risk ratio; AOD, airway obstructive disease.

Seventh Day Adventist cohort. The SDA cohort contained no smokers (only nonsmokers and ex-smokers and included respiratory symptom data as well as mortality information over a 10-year period. The bulk of the study participants were in three areas in California (Los Angeles, San Diego, and San Francisco) (*5,6*). Exposure estimates included length of residence and more than one area monitor per person, and accounted for time spent at place of residence and job, as well as environmental tobacco smoke exposure. In a series of reports on the SDA cohort, a wide range of air pollutants besides PM were also assessed. In the SDA cohort, exposure is closer to individual-level exposure than in either the Six Cities or ACS cohorts.

In the SDA cohort, the RR for mortality associated with PM_{10} was not significant and was said to be around 1.0 (*6*). The RR for mortality associated with $PM_{2.5}$ (based on visibility) was "close to, or less than, one" (*6*). The relative risk of developing new cases of airway obstructive disease (AOD), chronic bronchitis, and chronic productive cough were significantly associated with PM_{10} (RR = 1.17). The association was not significant for asthma or cough (*5*).

The lack of an association for mortality is not consistent with the Six Cities and ACS cohorts. The presence of an association for morbidity, but not mortality, does not provide a coherent argument for mortality. However, morbidity is the more sensitive indicator of an effect, which is consistent with the coherence criterion (*40*).

Even the association with symptoms is problematic. Logistic regression results were provided for new cases of AOD, chronic bronchitis, and asthma. However, reversal of these symptoms also occurred, as 34% to 51% of the symptoms went away between 1977 and 1987 (Table 4).

If PM is also associated with reversal of symptoms, a causal association is unlikely because it is hard to imagine that PM_{10} air pollution could be causally associated with both new symptoms and reversal of symptoms. Separate analyses to account for reversibility of symptoms should analyze the correlation of 1977–1987 PM_{10} concentration with new cases and with symptom reversals to see if there is a positive association with the former and a negative association with reversals. These results are not reported.

Finally, the PM_{10} group-level risk estimates for AOD and chronic bronchitis are over 40 times greater than the estimates based on individual-level smoking data from the same cohort (see Appendix 2). Thus, the group-level PM_{10} risk estimates for symptoms in this cohort appear to be high.

Six Cities cohort. Several studies have assessed the respiratory health of children in the Six Cities study (*41,42*). Both evaluated the same cohort of preadolescent school children, but $PM_{2.5}$ measurements are available only for the later study (*42*), which was analyzed as a cross-sectional study and used 12 months of $PM_{2.5}$ data as the exposure variable (annual mean). Relative odds were calculated comparing the most polluted (Steubenville) and least polluted (Topeka) cities after adjustment for sex, age, maternal smoking, and use of a gas stove. There were no significant associations of respiratory symptoms or lung function with $PM_{2.5}$ (except hay fever, which showed a negative relationship). RR estimates were elevated about twofold for bronchitis, chronic cough, and chest illness. The widest 95% confidence interval (CI) and highest RR was for chronic cough (RR = 2.3; CI = 0.4, 13.2). There was "no evidence for an effect" of pollution exposure on any measure of lung function, even in children with persistent wheeze, despite use of potentially more sensitive measures of small airways response than FEV_1 and FVC (*42*). Children generally spend more time outdoors than adults and have a greater specific ventilation (liters per kilogram body mass).

The adjustments for potential confounders may not be adequate. For example, the RRs were not adjusted for season, although the RR for bronchitis associated with PM_{15} was reduced from 2.52 to 1.97 when such an adjustment was made. Also, Dockery et al. (*42*) suggested that effects of acute exposure occurring before examination may have masked any chronic effects. The cross-sectional study design may not provide sufficient power to detect significant differences.

PM3001135208

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

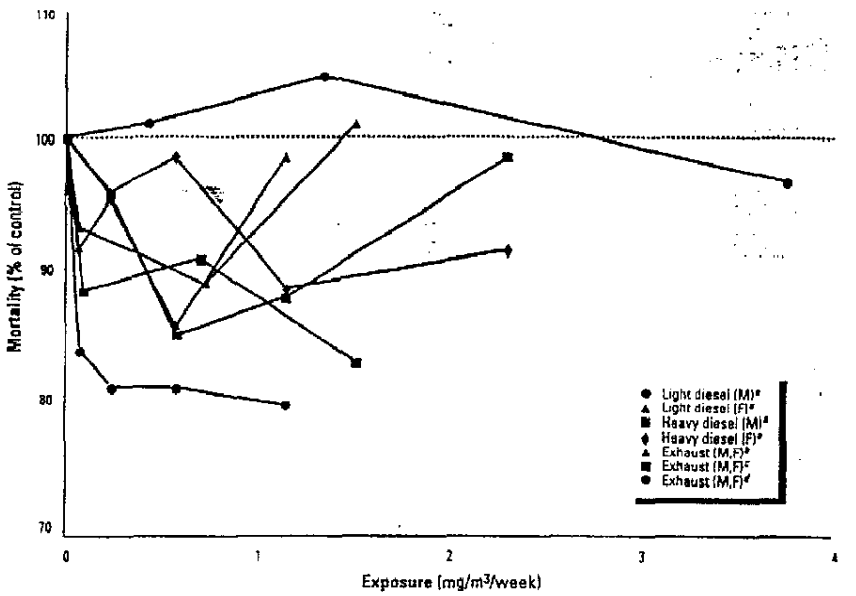

Figure 5. Percent mortality in lifetime exposure of rats to diesel exhaust. Abbreviations: M, male; F, female. The dashed line indicates controls.
[a]Data from Ishinishi et al. (*48*).
[b]Data from Mauderly et al. (*50*).
[c]Data from Mauderly et al. (*52*).
[d]Data from Heinrich et al. (*54*).

Summary

The coherence and consistency criteria were not met using either individual-level or ecological-level data. The individual-level data suggested a possible threshold effect at or below about five cigarettes per day on lung function (from Six Cities data), as well as coronary heart disease and respiratory disease mortality (*39*). The $PM_{2.5}$ concentration difference between high and low polluted cities was more than two orders of magnitude below the threshold, and any effect of the long-term exposure to these concentrations on lung function was undetectable.

Using group-level data from the SDA cohort, the coherence criterion was not met because 1) there was no $PM_{2.5}$/mortality association; 2) the PM_{10}/symptom associations showed an implausibly high strength of association; and 3) the long-term biological significance of the symptoms was unclear, given the high frequency of symptom reversal and the lack of any analysis showing no association between $PM_{2.5}$ and symptom reversal.

Biological Plausibility

Are the results biologically plausible and do they agree with current understanding of how organisms respond to low concentrations of PM?

Plausibility is not a required criterion to demonstrate causality. However, if ecologic study designs are being used to both generate and test the hypothesis as well as for risk assessment, then biological plausibility takes on added importance. An increased level of proof is required because ecologic studies are subject to the ecologic fallacy, and the smoking analogy indicates large overestimates of risk.

There appears to be general agreement that no plausible mechanism is presently available to explain the associations between chronic exposure to $PM_{2.5}$ air pollution and increased mortality. Pope et al. (*4*) indicated that additional research is needed to "help a toxicologic framework for interpreting these [ACS] findings."

The hypothesis predicts that long-term exposure to fine particulate should increase mortality. There are experimental data of lifetime exposure of animals to fine particulate matter showing no increased mortality even though exposures are so high as to produce lung overload (submicron diesel particulate was used as the fine particulate). Exposure was adjusted to reflect average 168-hr weekly exposures, which is analogous to an annual average. Despite average concentrations of diesel exhaust particulate up to 100 times higher than the most polluted city in the Six Cities study, mortality was not increased (*43*) (see Appendix 3 and Fig. 5, which summarize these results). These concentrations are so high that overloading occurred, causing reduced clearance, increased retention of particulate matter, and increased lung burden.

Green and Watson (*44*) reviewed existing data regarding issues critical in evaluating the toxic effects of small PM (primarily diesel exhaust) at ambient levels. I have summarized their major points as they relate to the biological plausibility of $PM_{2.5}$ air pollution. Retention of PM in the lung increases in the working environment as milligram per cubic meter PM concentrations increase (as in pneumoconiosis). Lung overload occurs when the deposition of PM over extended periods of time overwhelms lung clearance and occurs only at higher exposures. Because the relationship of exposure and retention may not be linear, the lung burdens at low exposure concentrations are less than would be predicted based on linear extrapolation from high PM exposures. Models based on experimental data predict that lung clearance declines as continuous exposure (24 hr/day, 7 days/week for 1–10 years) increases from 100 $\mu g/m^3$ to 1,000 $\mu g/m^3$. Under continuous exposure conditions, the models predict no reductions in alveolar clearance of diesel particulate in adults or children below daily concentrations of 50 $\mu g/m^3$. The models predict that if exposure is intermittent, clearance overload would not occur at concentrations below 1,000 $\mu g/m^3$.

Human exposure is likely to be intermittent, and concentrations of $PM_{2.5}$ above even 50 $\mu g/m^3$ are unlikely to occur. The 95th percentile daily concentration in the Six City study was 43 $\mu g/m^3$ (*45*). Thus, impaired clearance and increased lung burden due to $PM_{2.5}$-induced overload are unlikely to occur.

Pritchard (*46*) suggested that overload also occurs in humans when human exposures are such that lung burdens approach those seen in animal experiments. It has been estimated that smokers of 25 middle-tar cigarettes (18 mg) per day with somewhat reduced clearance rates would achieve a lung burden such that tar clearance and deposition would be in equilibrium (*46*). By this estimate, overload in a heavy smoker would occur with exposure to daily concentrations of about 25,000 $\mu g/m^3$ mainstream tobacco smoke.

In sum, there is evidence that chronic exposure concentrations of $PM_{2.5}$ several orders of magnitude higher than ambient air concentrations may have little effect on mortality in experimental studies of rodents. Survival is similar at low exposure levels and under conditions of lung overload when compared to control exposures. Thus, there appears to be a no-effects threshold. There is little support for the plausibility of lifetime $PM_{2.5}$ exposures in microgram per cubic meter concentrations

PM3001135209

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

causing increased mortality in humans based on experimental exposure in rodents.

Risk Assessment

Hertz-Picciotto (*47*) suggested a classification framework for using epidemiological studies in quantitative risk assessment and in setting air quality standards. These classifications are briefly summarized in Table 5, along with comments pertaining to whether the $PM_{2.5}$ studies meet the suggested requirements. The EPA (*18*) endorses the use of these criteria in contributing to the weight-of-evidence determination of a human health hazard.

The EPA position on the need for individual-level exposure data is somewhat ambiguous. The EPA only has regulatory authority over outdoor air and argues that variations in ambient PM are reflected in variations in personal PM exposure and that ambient PM is "hypothesized to create the health effects" (*18*). Therefore, reduction in ambient PM will "help to protect the public from adverse health outcomes associated with personal exposure to ambient PM" (*18*). Thus, there is no need for E-R trends based on individual-level exposures.

The opposing side to this argument is discussed primarily in the section on ecologic study design. The contribution of ambient PM to personal PM is small for a majority of the population, and the health effects are probably too small to measure in individuals or populations. The EPA has also presented statements suggesting that quantification of individual-level exposure may be necessary. Personal exposure is said to be "important in itself, because the body may react differently to ambient and nonambient particles" (*19*). Personal PM may act as a confounder in ecological studies, and personal PM is a "critical parameter...[when] health outcomes are being tracked individually" (*19*).

As shown in Table 5, none of the Hertz-Picciotto criteria for quantification of risk and setting air quality standards using epidemiology studies are met.

The first and fifth criteria are the strength of association and biological gradient causal criteria outlined by Hill (*8*). These were discussed above where it was suggested that the group-level strength of association was exaggerated and the biological gradient (E-R) could not be determined because of uncontrolled confounding and inadequate estimate of exposure. The third criterion is not met because it is likely that various factors may be confounding the associations reported in the Six Cities and ACS studies. Physical inactivity and FEV_1 were identified as two examples of confounders. Issues of confounding and other biases increase in importance when an association is weak, as it is for PM air pollution. The fourth criterion is that individual-level exposure data are necessary to avoid the possibility of exposure misclassification bias and the ecological fallacy. There are no individual-level exposure data to determine whether persons with increased mortality also have increased $PM_{2.5}$ exposure. Because group-level exposure cannot be linked quantitatively with individuals and is often only a small proportion of total exposure, the fourth criterion is not met. Not only are none of the criteria met, the risk estimates for ambient $PM_{2.5}$ appear to be biased upward.

Table 5. Criteria for using epidemiology studies in quantitative risk assessment

Criteria[a]	Requirement[a]	Does prospective cohort design meet the criteria?
Moderate to strong positive association present	Necessary	Unlikely: Strength of association in prospective cohort studies is weak, and risk is an overestimate as determined by validity check with individual-level data from smokers. In the SDA study, there is no association with PM.
Strong biases ruled out or unlikely; includes consideration of study design, validity of measure of exposure, and outcome	Necessary	No: Exposure misclassification bias is very likely and ecological fallacy probable. Ecological study design is inappropriate for testing hypothesis or evaluating E-R and requires individual-level design to assess consistency of results. Risk estimates are overestimates in Six Cities and ACS studies as determined by comparison of individual-level data from smoking data.
Confounding controlled or likely to be limited	Necessary	No: There are substantial differences between cities in risk factors that are not adjusted for in the analysis (e.g., physical activity, diet, blood pressure, SES). These differences could by themselves explain the difference between high and low polluted cities.
Quantification of exposure linked to individuals	Necessary	No: Exposure is based on single number for all inhabitants of the study area and is thus a group-level measure and not linked to any individual. The prospective cohort mortality studies need a cumulative exposure estimate that includes both concentration and time. The estimates used have no time variable, only average concentration, which has changed over time. Ambient $PM_{2.5}$ is for many individuals only a small proportion of total $PM_{2.5}$ exposure and may therefore wash out possible effects of ambient $PM_{2.5}$.
Monotonic E-R relationship	Not necessary, but adds certainty to risk estimates	Can't tell: E-R relationship cannot be determined because exposure is misclassified and confounding is present.

Abbreviations: SDA, Seventh Day Adventists; PM, particulate matter; E-R, exposure–response; ACS, American Cancer Society; SES, socioeconomic status.
[a]Criteria and requirement from Hertz-Picciotto (*47*).

Summary and Conclusion

Several aspects of the prospective cohort studies of $PM_{2.5}$ air pollution (*3,4*) render them susceptible to error in estimating individual risk and suggest that the associations may be statistical and not causal.

Group-level exposures make these prospective cohort studies susceptible to error in estimating individual risk. Ambient exposure is poorly correlated with personal exposure. Differences between individuals in the same city are larger than individual differences between cities. Long-term changes in air pollution levels are not reflected in group-level exposure estimates. Exposure to mainstream and possibly sidestream cigarette smoke probably masks out any potential to measure exposure effects to ambient $PM_{2.5}$. Ambient concentrations do not reflect personal exposure on a day-to-day or year-to-year basis, do not reflect long-term or lifetime exposure, and are often only a small portion of total personal $PM_{2.5}$ exposure. Ambient concentrations were measured too close to time of death to be causally linked to chronic mortality. Thus, the temporality criterion, the one criterion that must be met to establish causality, is not met.

The $PM_{2.5}$ RRs for total and cardiopulmonary mortality are orders of magnitude too high when tested using the tobacco analogy. That is, group-level data from the Six Cities and ACS cohorts suggest that $PM_{2.5}$ is 35–1,000 times more toxic than smoke from a low-tar cigarette on a weight/volume basis. This is a conservative estimate, as most smokers smoke cigarettes with more tar, and low-tar cigarettes have been available only recently in the life span of study subjects.

Even if $PM_{2.5}$ were as toxic as cigarette smoke PM, the prospective study design could

PM3001135210

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Table 6. Summary of weight of evidence regarding a causal association

Criteria	Effects on causal hypothesis
Chance	Supports because statistical significance is achieved
Confounding	Detracts due to inadequate adjustment for potential confounders
Bias	Detracts, with misclassification of exposure as best known bias
Strength of association	Detracts because association is weak due, in part, to very low exposure (risk = exposure × toxicity)
Exposure–Response	Detracts because trends are not plausible based on comparison with individual-level smoking data
Consistency	Detracts because results are contrary to individual-level studies of smokers
Coherence	Detracts because morbidity (pulmonary function test) should show stronger association than mortality
Analogy	Detracts, as risk is overestimated compared to tobacco combustion products
Biological plausibility	Detracts because there is no increased mortality of animals exposed for lifetime to high concentrations of combustion products
Temporality	Eliminates possibility of causal associations because estimates of exposure either do not precede disease or do not provide adequate latency

not detect a measurable difference because of the relatively small concentration differences between high and low polluted cities.

Confounding from variations in risk factors between cities requires adjustments that have not been made. At least two confounders (physical inactivity and FEV_1) have been identified that appear to bias the $PM_{2.5}$ risk estimates away from the null. Analysis of individual-level lung function data from the Six Cities cohort shows that the effect of ambient $PM_{2.5}$ is too small to have an independent measurable effect on FEV_1. Thus, the observed association of $PM_{2.5}$ and mortality may be in large part explained by unadjusted confounding.

The biases inherent in group-level estimates of exposure (exposure misclassification bias) and the unadjusted confounding provide both theoretical and demonstrated reasons for questioning the validity of the E-R trend. The tobacco analogy demonstrations of gross overestimates of the RRs are examples of the ecologic fallacy.

The coherence criterion is not met because the ambient $PM_{2.5}$ concentrations are too low to produce a measurable effect on lung function. Changes in lung function are considered to be more sensitive indicators of adverse effects than death. Thus, because the small differences in $PM_{2.5}$ between high and low polluted cities do not produce measurable differences in lung function, it is unlikely that they would produce measurable differences in mortality.

The plausibility criterion is not met because rodents exposed for a lifetime to high concentrations of a mixture containing fine PM often show no reduction in life span, even though overloading results in reduced clearance. Overloading and lung burden in humans are improbable events at low microgram per cubic meter concentrations in ambient air.

In sum, the prospective cohort studies investigating the association of mortality and chronic exposure to $PM_{2.5}$ do not demonstrate a causal association with increased mortality. Risk estimates from these studies are exaggerated, and these investigations do not meet the criteria for a quantitative risk assessment.

The weight of the evidence is not sufficient to support the hypothesis of a causal association (Table 6).

Appendix 1

Methodology and sample calculations for comparing $PM_{2.5}$ risk estimates based on group-level exposure and individual-level cigarette smoke exposure from the Six Cities (3) and ACS (4) cohorts

Both the Six Cities and ACS studies show significant associations between average $PM_{2.5}$ concentrations and mortality after adjustment for individual risk factors using Cox proportional hazards regression models. The risk ratios (RR) from the regression model is calculated as follows:

$$RR = \exp(\beta \times \text{exposure}) \quad (1)$$

The RR for total mortality in the ACS cohort is 1.17, and the difference between high and low polluted areas is 24.5 $\mu g/m^3$. Substituting in Equation 1 and solving for the regression coefficient β gives a value of 0.0064 for β in the ACS cohort..

Both the Six Cities and ACS cohort studies evaluated individual-level risk for a 25 pack-year smoker (based on 20 cigarettes/day for 25 years in the ACS study). A pack per day smoker smoking low-tar cigarettes (0.5 mg tar) is exposed to a daily annual average of about 556 $\mu g/m^3$ (0.5 mg/cigarette × 20 cigarettes/day × 18 m^3 air breathed/day). Substituting $\beta = 0.0064$ and exposure = 556 $\mu g/m^3$ in equation 1 gives a RR of 35.1, which is the RR for a low-tar smoker based on the group-level $PM_{2.5}$ coefficient.

Another procedure is to calculate how many times greater the exposure of the cigarette smoker is to Δ (most polluted city vs. least polluted city) and raise the RR to that power. That is, RR for $\Delta = 1.17$. Exposure of smoker/Δ = (556 $\mu g/m^3$)/(24.5 $\mu g/m^3$) = 22.7. This is how many times higher exposure a pack/day smoker of low-tar cigarettes has than a resident of high polluted areas compared to low polluted areas in the ACS cohort. RR for smoker based on group-level $RR = 1.17^{22.7} = 35.3$ (slight differences are due to rounding differences in the calculation).

Table A1-1 summarizes the group-level exposures of high versus low polluted cities for Six Cities and ACS cohorts as well as individual-level exposure for pack/day smokers of low-tar and average-tar cigarettes. RRs of total and cardiopulmonary mortality for current smokers derived from group-level and individual-level data from Six Cities and ACS cohorts are summarized in Table A1-2.

Clearly, the ecological based risks derived from group-level exposures are orders of magnitude higher than the risk estimates derived from individual-level exposures. The smallest difference is when the individual-level risk is 2.07, compared to a RR of 35.3 based on $PM_{2.5}$ toxicity from group-level data. For the average smoker of a 15-mg tar cigarette, the difference is 2.07 versus 32×10^{45}. It is not plausible that $PM_{2.5}$ air pollution is that much more toxic than cigarette smoke.

Continued next page

PM3001135211

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Appendix 1 (continued)

A third procedure is to calculate the risk on a per microgram per cubic meter basis, i.e., ln $RR/\Delta PM_{2.5}$. This coefficient can be used for any or all of the following demonstrations:

Assume an 18.6 $\mu g/m^3$ $PM_{2.5}$ group-level difference in exposure and RR of 1.26 for total mortality in the Six Cities cohort. Individual-level exposure for an average 20 cigarettes/day smoker of 15-mg tar cigarettes is about 16,700 $\mu g/m^3$.

Group-level estimate of total mortality for 1 $\mu g/m^3$ $PM_{2.5}$ = $_c$ (ln 1.26/18.6 $\mu g/m^3$) = 1.01 per $\mu g/m^3$.

Estimate of risk of total mortality for 1 $\mu g/m^3$ $PM_{2.5}$ based on individual-level risk estimates for an average smoker = $_c$ (ln 2.00/16,700 $\mu g/m^3$ = 1.00004 per $\mu g/m^3$).

Comparative toxicity of $PM_{2.5}$ to tobacco smoke PM = (ln 1.26/18.6 $\mu g/m^3$) ÷ (ln 2.0/16,200 $\mu g/m^3$) = 299.

This method of calculation is also displayed in Table 2 in the text.

Table A1-1. Annual exposure to $PM_{2.5}$ air pollution (most vs. least polluted city) and from 20 cigarettes/day

$PM_{2.5}$ source	$PM_{2.5}$ ($\mu g/m^3$)
Six Cities study (Steubenville/Portage)	18.6
ACS study	24.5
Smoker	
Low-tar cigarette (0.5 mg)	556
Cigarette (15 mg tar)	16,700

ACS, American Cancer Society.

Table A1-2. Comparison of risks of total and cardiopulmonary mortality risks of smokers derived from individual-level and group-level data

		Increase in risk for current smoker		
		Group-level analysis		Individual-level analysis
Study RR[a]		(0.5 mg × 20 cig/day)	(15 mg × 20 cig/day)	(25 pack-year smoker)
Total mortality				
Six Cities	1.26	1,000	1.4×10^{90}	2.00 (1.51–2.65)
ACS	1.17	35.3	32×10^{45}	2.07 (1.75–2.43)
Cardiopulmonary mortality				
Six Cities	1.37	12,200	(out of range of calculator)	2.30 (1.56–3.41)
ACS	1.31	459	95×10^{78}	2.28 (1.79–2.91)

Abbreviations: cig, cigarette; ACS, American Cancer Society.
[a]Relative risk of high versus low polluted cities.

Appendix 2

Methodology and sample calculations for comparing PM_{10} risk estimates for respiratory symptoms among ex-smokers based on group-level exposure to PM_{10} and individual-level cigarette smoke exposure from the SDA cohort (5)

Abbey et al. (5) estimated risk of respiratory symptoms [airway obstructive disease (AOD), chronic bronchitis, and asthma] with ambient PM_{10}. Relative risk (RR) associated with 1,000 hr/year (42 days) exposure to PM_{10} was 1.17 for AOD and 1.21 for cough. RR estimates using mean exposure to PM_{10} were also provided and will be used in the comparisons.

Logistic regression coefficients for both symptom categories were not significant for mean concentrations above 40, 50, and 60 $\mu g/m^3$, but AOD was significant for a mean annual ambient concentration of 70 $\mu g/m^3$. The RRs were based on PM_{10} concentrations for the years 1973–1977. Health outcomes were new cases occurring during the years 1977–1987.

All cohort members were either nonsmokers or ex-smokers. Ex-smokers had to have stopped smoking sometime before 1977. Data on intensity of smoking were not provided; however, a regression coefficient for years of smoking was provided. The average number of years smoked was about 15 years. However, because PM_{10} exposure was based on the annual average between 1973–1977, only 4 years of smoking will be used in the following examples.

A sample calculation for AOD is as follows:

RR = exp (β × exposure).

Group-level RR of AOD (and chronic bronchitis) associated with annual average of 70 $\mu g/m^3$ = 1.62.
β = ln 1.62/70 $\mu g/m^3$ = 0.00689.

Individual-level RR of AOD for ex-smoker associated with smoking 4 years = exp (β × 4 yrs) = 1.09, where β = 0.021522.

Exposure of ex-smoker: 20 cigarettes/day (low-tar cigarette) = 556 $\mu g/m^3$.
Exposure of ex-smoker: 20 cigarettes/day (15 mg tar cigarette) = 16,666 $\mu g/m^3$.

Risk of AOD for ex-smoker derived from group-level PM_{10} risk estimate:
Low-tar cigarette = exp (β × exposure) = exp (0.00689 × 556) = 46.1.
Average cigarette = exp (0.00689 × 16,666) = 7×10^{49}.

Table A2-1. Individual-level estimate of risk of smoking compared to group-level estimate of PM_{10} in cohort study of Seventh Day Adventists (5)

Variable	Individual-level RR for ex-smoker	Ex-smoker smoking 20 cigarettes/day[b]	
		Low tar (0.5 mg)	Average tar (15 mg)
Exposure (4 years)		556 $\mu g/m^3$	16,666 $\mu g/m^3$
New cases 1977–1987			
AOD[a]	1.09	46.1[b]	7.6×10^{49}[b]
Chronic bronchitis	1.12	46.1[b]	7.6×10^{49}[b]

Abbreviations: RR, risk ratio; cig, cigarettes; AOD, airway obstructive disease. These RRs are the same order of magnitude as those derived for smokers' risk and $PM_{2.5}$ from the Six Cities and American Cancer Society cohorts.
[a]Definite symptoms of AOD if had one or more of the following: 1) definite chronic bronchitis symptoms (cough and/or sputum on most days for at least 3 months/year for 2 years or more; 2) definite asthma (diagnosed by physician, history of wheezing); 3) emphysema (diagnosed by physician, shortness of breath when walking or exercising)
[b]Group-level PM_{10} RR.

The comparison for the two symptom categories are summarized in Table A2-1.

PM3001135212

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

Appendix 3

Summary of experimental studies of long-term exposure of animals to combustion source fine particulate

Reference	Species/protocol	Exposure group[a] (mg/m^3)	Survival (%)			Comments
Ishinishi et al. (*48*)	Fisher 344/Jcl rats; 16 hr/day, 6 days/week, 30 months; 0.1, 0.4, 1, 2 mg/m^3 LD and 0.4, 1, 2, 4 mg/m^3 HD DE	Control LD diesel 0.06 0.23 0.57 1.14 HD diesel 0.23 0.57 1.14 2.3	27/31[b] 39/37[b] 41/34[b] 41/41[b] 42/32[b] 30/34[b] 38/32[b] 36/39[b] 28/37[b]			Longer survival in exposed than control animals
Lewis et al. (*49*)	F-344 rats, monkeys (M); 7 hr/day, 5 days/week, 24 months; 2 mg/m^3 coal dust, 2 mg/m^3 DE, 1.1 mg/m^3 coal dust + DE	Control Coal dust (0.042) DE (0.42) DE + coal dust (0.42)				No difference in survival
Mauderly et al. (*50*)	F-344 rats; 7 hr/day, 5 days/week, 30 months; 0.35, 3.5, and 7.1 mg/m^3 DE	Control 0.07 0.73 1.5	60[c] 62.8[c] 64.4[c] 59.6[c]			No significant difference in BW, survival; no overt signs of toxicity
Heinrich et al. (*51*)	Golden hamsters, NMRI mice, Wistar rats; 19 hr/day, 5 days/week, 4.24 mg/m^3 120 weeks (hamsters, mice) and 140 weeks (rats)	Control DE without PM 2.4 mg/m^3	Hamsters (M/F) 25/2 33/0 27/8	Mice (F) 22 37 5	Rats (F) 46 42 40	Clearance compromised in rats; wet-tail disease mortality in hamsters
Mauderly et al. (*52*)	F-344 rats (M and F); 7 hr/day, 5 days/week, 30 months; 0.35, 3.5, and 7.1 mg/m^3 DE	Control 0.07 0.7 1.5	44.7[c] 51.2[c] 49.8[c] 54.3[c]			No significant differences in BW or survival
Mauderly et al. (*53*)	CD-1 mice; 7 hr/day, 5 days/week, 30 months; 0.35, 3.5, and 7.1 mg/m^3 DE	Control 0.07 0.7 1.5	Median days M/F 550/620 490/650 450/600 561/630	All 600 580 540 570		Percent survival not reported
Heinrich et al. (*54*)	Wistar rats; 18 hr/day, 5 days/week, 24 months exposure, 6 months no exposure; 0.8, 2.5, and 7 mg/m^3 DE	Control 0.43 1.34 3.75	15[c] 14[c] 11[c] 18[c]			
Nikula et al. (*55*)	F-344 rats; 16 hr/day, 5 days/week, 24 months; 2.5 mg/m^3 DE, 6.5 mg/m^3 carbon black	Control DE 1.19 3.1 Carbon black 1.19 3.0	13.8/35.6[b] 14.4/30.9[b] 5.8/26.7[b] 4.3/40.4[b] 0.7/25.9[b]			
Mauderly et al. (*56*) ty	F-344/Crl normal and (elastase-induced) emphysematous rats; 7 hr/day, 5 days/week, 24 months	Control 0.73 (normal) 3.5 (emphysematous)				No significant effect of DE on mortality, BW, or morbid- of normal or emphysema- tous rats
Karagianes et al. (*57*)	Wistar rats; 6 hr/day, 5 days/week, 20 months; 8.3 mg/m^3 DE, 6.6 and 14.9 mg/m^3 coal dust, 8.3 and 5.8 mg/m^3 DE + coal dust	Control DE (1.8 mg/m^3) Diesel + coal dust (1.8 + 1.04 = 2.4) Coal dust (1.2) Coal dust (2.7)				No significant effect on mortality or BW

Abbreviations. LD, light duty; HD, heavy duty; DE, diesel exhaust; M, male; F, female; PM, particulate matter; BW, body weight.

[a]Average long-term exposure was calculated for each exposure group as follows: (hours exposed per week/168 hours per week) × concentration (mg/m^3).

[b]Male/female

[c]Male and female combined

PM3001135213

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001

References and Notes

1. Spengler J, Wilson R. Emissions, dispersion, and concentration of particles. In: Particles in Our Air: Concentrations and Health Effects (Wilson R, Spengler JD, eds). Cambridge, MA:Harvard University Press, 1996,41–62.
2. Office of Air Quality Planning and Standards. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. OAQPS staff paper (external review draft). Research Triangle Park, NC:U.S. Environmental Protection Agency, 1996.
3. Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759 (1993).
4. Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674 (1995).
5. Abbey DE, Hwang BL, Burchette RJ, Vancuren T, Mills PK. Estimated long-term ambient concentrations of PM_{10} and development of respiratory symptoms in a nonsmoking population. Arch Environ Health 50:139–152 (1995).
6. Abbey DE, Lebowitz MD, Mills PK, Petersen FF, Beeson WL, Burchette RJ. Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. Inhal Toxicol 7:19–34 (1995).
7. Taubes G. Epidemiology faces its limits. Science 269,164–169 (1995).
8. Hill AB. The environment and disease: association or causation? Proc R Soc Med 58:295–300 (1965).
9. Brenner H, Savitz DA, Jöckel K, Greenland S. Effects of nondifferential exposure misclassification in ecologic studies. Am J Epidemiol 135:85–95 (1992).
10. Greenland S. Divergent biases in ecologic and individual-level studies. Stat Med 11:1209–1223 (1992).
11. Piantadosi S, Byar DP, Green SB. The ecological fallacy. Am J Epidemiol 127:893–904 (1988).
12. Abbey DE, Burchette RJ. Relative power of alternate ambient air pollution metrics for detecting chronic health effects in epidemiological studies. Environmetrics 7:453–470 (1996).
13. Spengler JD, Dockery DW, Turner WA, Wolfson JM, Ferris BG. Long-term measurements of respirable sulfates and particles inside and outside homes. Atmos Environ 15:23–30 (1981).
14. Spengler JD, Treitman RD, Tosteson TD, Mage DT, Soczek ML. Personal exposures to respirable particulates and implications for air pollution epidemiology. Environ Sci Technol 19:700–707 (1985).
15. Ozkaynak H, Xue J, Weker R, Butler D, Spengler J. The Particle Team (P Team) study: Analysis of the Data. Final report, Vol 3. EPA/600/R-95. Washington, DC:U.S. Environmental Protection Agency, 1995.
16. Mage DT, Buckley TJ. The relationship between personal exposures and ambient concentrations of particulate matter. 95-MP 18.01. Presented at the 88th Annual Meeting and Exhibition of the Air and Waste Management Association, 18–23 June 1995, San Antonio, TX.
17. Brown K, Paxton M, Wyzga R. The relationship between personal exposure to airborne particulate matter (PM_{25} and PM_{10}) and indoor and outdoor concentrations from studies conducted in four cities [Abstract]. Presented at Health Effects of Particulate Matter in Ambient Air. International Symposium, 23–25 April 1997, Prague.
18. U.S. EPA. Responses to Significant Comments on the 1996 Proposed Rule on the National Ambient Air Quality Standards for Particulate Matter. Docket number A-95-54 (13 December 1996; 61FR65638). Washington, DC:U.S.Environmental Protection Agency, 1997.
19. U.S. EPA. Air Quality Criteria for Particulate Matter. EPA-600-AP-95-001C. Washington, DC:U.S. Environmental Protection Agency, 1996.
20. Darlington TL, Kahlbaum DF, Heuss JM, Wolff GT. Analysis of PM_{10} trends in the United States from 1988 through 1995. J Air Waste Manage Assoc 47:1070–1078 (1997).
21. Greenland S, Robins J. Invited commentary: Ecologic studies—biases, misconceptions, and counterexamples. Am J Epidemiol 139:747–760 (1994).
22. Piantadosi S. Invited commentary: Ecologic biases. Am J Epidemiol 139:761–764 (1994).
23. HEW. Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service. Public Health Service Publication No. 1103, Washington, DC:Department of Health, Education, and Welfare, 1964.
24. National Center for Health Statistics. Prevention Profile. Health, United States, 1989. Hyattsville, MD:U.S. Public Health Service, 1990.
25. Repace JL, Lowrey AH. A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Environ Int 11:3–22 (1985).
26. HHS. Reducing the Health Consequences of Smoking, 25 Years of Progress. a Report of the Surgeon General. DHHS Publication No. (CDC) 89-8411. Washington, DC:U.S. Department of Health and Human Services, 1989.
27. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 38: Tobacco Smoking. Lyon:International Agency for Research on Cancer, 1986.
28. Hinds WC. Size characteristics of cigarette smoke. Am Ind Hyg Assoc J 39:48–54 (1978).
29. Wynder EL. Epidemiological issues in weak association. Int J Epidemiol 19(suppl 1):S5–S7 (1990).
30. Wynder EL. Workshop on guidelines to the epidemiology of weak association. Prev Med 16:139–141 (1987).
31. Strachan DP. Ventilatory function, height, and mortality among lifelong non-smokers. J Epidemiol Community Health 46:66–70 (1992).
32. Weiss ST, Segal MR, Sparrow D, Wager C. Relation of FEV, and peripheral blood leukocyte count to total mortality. Am J Epidemiol 142:493–503 (1995).
33. Dockery DW, Ware JH. Distribution of forced expiratory volume in one second and forced fital capacity in healthy white, adult never-smokers in six U.S. cities. Am Rev Respir Dis 131:511–520 (1985).
34. Ferris BG Jr, Speizer FE, Spengler JD, Dockery D, Bishop YMM, Wolfson M, Humble C. Effects of sulfur oxides and respirable particles on human health: methodology and demography populations in study. Am Rev Resp Dis 120:767–779 (1979).
35. Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BG. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. Am Rev Respir Dis 146:1345–1348 (1992).
36. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee I-M, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. N Engl J Med 328:538:545 (1993).
37. Liptert FW. Estimating air pollution—mortality risks from cross-sectional studies: prospective vs. ecologic study design, in particulate matter. In: Health and Regulatory Issues. 78-102. Proceedings of the International Specialty Conference, Pittsburgh, PA. 1995. Pittsburgh, PA:Air and Waste Management Association, 1995.
38. Dockery DW, Speizer FE, Ferris BG Jr, Ware JH, Louis TA, Spiro A. Cumulative and reversible effects of lifetime smoking on simple tests of lung function in adults. Am Rev Respir Dis 137:286–292 (1988).
39. Gori GB, Mantel N. Mainstream and environmental tobacco smoke. Regul Toxicol Pharmacol 14:88–105 (1991).
40. Bates DV. Health indices of the adverse effects of air pollution: the question of coherence. Environ Res 59:336–349 (1992).
41. Ware JH, Ferris BG, Dockery DW, Spengler JD, Stram DO, Speizer FE. Effect of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am Rev Respir Dis 133:834–842 (1986).
42. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 139:587–594 (1989).
43. Watson AY, Green GM. Noncancer affects of diesel emissions: animal studies. In: Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. A special report of the institute's diesel working group. Cambridge, MA:Health Effects Institute, 1995;139–164.
44. Green GM, Watson AY. Relation between exposure to diesel emissions and dose to the lung. In: Diesel Exhaust. A Critical Analysis of Emissions, Exposure, and Health Effects. A special report of the institute's diesel working group. Cambridge, MA:Health Effects Institute, 1995,165–184.
45. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? J Air Waste Manage Assoc 46:927–939 (1996).
46. Pritchard JN. Dust overloading causes impairment of pulmonary clearance: evidence from rats and humans. Exp Pathol 37:39–42 (1989).
47. Hertz-Picciotto I. Epidemiology and quantitative risk assessment: a bridge from science to policy. Am J Public Health 85:484–491 (1995).
48. Ishinishi N, Kuwabara N, Nagase S, Suzuki T, Ishiwata S, Kohno T. Long-term inhalation studies on effects of exhaust from heavy and light duty diesel engines on F344 Rats. In: Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust (Ishinishi N, Koizumi A, McClellan RO, Stober W, eds). New York:Elsevier Science Publishing, 1986;139–164.
49. Lewis TR, Green FHY, Moorman WJ, Burg JR, Lynch DW. A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. J Am Coll Toxicol 8:345–375 (1989).
50. Mauderly JL, Jones RK, McClellan RO, Henderson RF, Griffith WC. Carcinogenicity of diesel exhaust inhaled chronically in rats. In: Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust (Ishinishi N, Koizumi A, McClellan RO, Stober W, eds). New York:Elsevier Science Publishing, 1986;397–410.
51. Heinrich U, Muhle H, Takenaka S, Ernst H, Fuhst R, Mohr V, Pott F, Stober W. Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. J Appl Toxicol 6(suppl 6):383–395 (1986).
52. Mauderly JL, Jones RK, Griffith WC, Henderson RF, McClellan RO. Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fundam Appl Toxicol 9:208–221 (1987).
53. Mauderly JL, Banas DA, Griffith WC, Hahn FF, Henderson RF, McClellan RO. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. Fundam Appl Toxicol 30:233–242 (1996).
54. Heinrich U, Fuhst R, Rittinghausen S, Crentzenberg O, Bellmann B, Koch W, Leusen K. Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol 7:533–556 (1995).
55. Nikula KJ, Snipes EB, Barr FB, Griffith WC, Henderson RF, Mauderly JL. Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F44 rats. Fundam Appl Toxicol 25:80–94 (1995).
56. Mauderly JL, Bice DE, Cheng YS, Gillett NA, Griffith WC, Henderson RF, Pickrell JA, Wolff RK. Influence of preexisting emphysema on susceptibility of rats to inhaled diesel exhaust. Am Rev Respir Dis 141:1333–1341 (1990).
57. Karagianes MT, Palmer RF, Busch RH. Effects of inhaled diesel emissions and coal dust in rats. Am Ind Hyg Assoc J 42:382–391 (1981).

PM3001135214

Source: https://www.industrydocuments.ucsf.edu/docs/hhhk0001